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(54) Title: SUBSTITUTED AZABICYCLO HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to a radio telephony network (1) supporting at least one link of a radio channel (6) for a packet data transmission service. The radio telephony network (1) comprises a plurality of network controllers (RNC). Each network controller (RNC) is connected, via an interface lub, to at least one base radio station (B-node) supervising at least one macrocell (5a). The radio telephony network (1) additionally comprises at least one base radio microstation (B1-micronode) connected to the network controller (RNC) via an interface lub of the same type as that connecting the base radio station (B-node) to said controller. The base radio microstation (B1-micronode) supervises at least one microcell (5b) incorporated in at least one macrocell (5a). The base radio microstation (B1-micronode) provides the packet data transmission service in the microcell (5b) on the link of the radio channel (6).

3,6-DISUBSTITUTED AZABICYCLO HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

5 This invention relates to derivatives of 3,6-disubstituted azabicyclo hexanes.

The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors.

10 The invention also relates to a process for the preparation of the compounds of the present invention, pharmaceutical compositions containing the compounds of the present invention and the methods of treating the diseases mediated through muscarinic receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated
15 by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. For example, the M_1 subtype is located primarily in neuronal tissues such as cerebral cortex and autonomic ganglia, the M_2 subtype is present
20 mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (Nature, 1986; 323: 411; Science, 1987; 237: 527). A review in Current Opinions in Chemical Biology, 1999; 3: 426, as well as in Trends in Pharmacological Sciences, 2001; 22: 409 by Eglen et. al., describe the biological potentials of modulating muscarinic receptor subtypes by
25 ligands in different disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease etc.

A review in J. Med. Chem., 2000; 43: 4333 by Christian C. Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous system and elaborates on muscarinic receptor structure and function, pharmacology and their
30 therapeutic uses.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in Molecules, 2001, 6: 142.

N.J.M. Birdsall et. al. in Trends in Pharmacological Sciences, 2001; 22: 215 have also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptors of knock out mice.

Muscarinic agonists such as muscarine and pilocarpine and antagonists such as atropine have been known for over a century, but little progress has been made in the discovery of receptor subtype-selective compounds making it difficult to assign specific functions to the individual receptors. Although classical muscarinic antagonists such as atropine are potent bronchodilators, their clinical utility is limited due to high incidence of both peripheral and central adverse effects such as tachycardia, blurred vision, dryness of mouth, constipation, dementia, etc. Subsequent development of the quarterly derivatives of atropine such as ipratropium bromide are better tolerated than parenterally administered options but most of them are not ideal anti-cholinergic bronchodilators due to lack of selectivity for muscarinic receptor sub-types. The existing compounds offer limited therapeutic benefit due to their lack of selectivity resulting in dose limiting side-effects such as thirst, nausea, mydriasis and those associated with the heart such as tachycardia mediated by the M₂ receptor.

Annual review of Pharmacological Toxicol., 2001; 41: 691, describes the pharmacology of the lower urinary tract infections. Although anti muscarinic agents such as oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these agents has been limited due to the side effects such as dry mouth, blurred vision and constipation. Tolterodine is considered to be generally better tolerated than oxybutynin. (W.D.Steers et. al. in Curr. Opin. Invest. Drugs, 2: 268, C.R. Chapple et. al. in Urology, 55: 33), Steers WD, Barrot DM, Wein AJ, 1996, Voiding dysfunction: diagnosis classification and management. In "Adult and Pediatric Urology," ed. JY Gillenwatter, JT Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstituted piperidine derivatives; WO 93/16018 and WO96/33973 are other close art references.

A report in J. Med. Chem., 2002; 44:984, describes cyclohexylmethyl piperidiny1 triphenylpropioamide derivatives as selective M₃ antagonist discriminating against the other receptor subtypes.

SUMMARY OF THE INVENTION

The present invention provides 3,6-disubstituted azabicyclo hexanes as muscarinic receptor antagonists and are useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems and process for the syntheses of the compounds.

The invention also provides pharmaceutical compositions containing the compounds, and which may also contain acceptable carriers, excipients or diluents which are useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

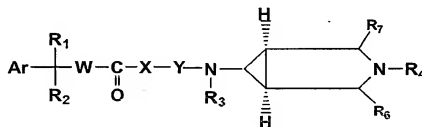
The present invention also includes within its scope prodrugs of the compounds. In general, such prodrugs are functionalized derivatives of these compounds which readily get converted *in vivo* into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known to the artisan of ordinary skill in the art.

The invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates, esters and metabolites of these compounds having the same type of activity.

The invention further includes pharmaceutical compositions comprising the compounds of the present invention, their enantiomers, diastereomers, prodrugs, N-oxides, polymorphs, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters or metabolites, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Other advantages of the invention will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect of the present invention, there are provided compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites,

wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), lower perhaloalkyl (C₁-C₄), cyano, hydroxy, nitro, halogen (e.g. F, Cl, Br, I), lower alkoxy (C₁-C₄), lower perhalo- alkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄);

R₁ represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R₂ represents alkyl, C₃-C₇ cycloalkyl ring which any 1-4 hydrogen atoms are substituted with halogen (e.g. F, Cl, Br, I), carbamoyl or lower alkyl;

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR or no atom wherein R represents hydrogen or C₁-C₆ alkyl;

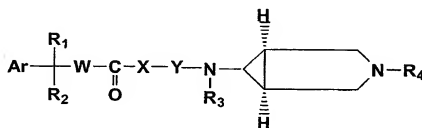
Y represents CHR₃CO wherein R₃ represents hydrogen, methyl or (CH₂)_q wherein q represents 0 to 4;

5 R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

R₆ and R₇ are independently selected from H, lower alkyl, COOH, CONH₂, NH₂, or CH₂NH₂; and

R₄ represents C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group
 10 independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxy, nitro,
 15 lower alkoxy, carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄).

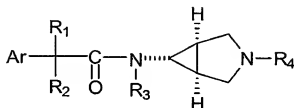
In accordance with a second aspect of the present invention, there are provided compounds having the structure of Formula II and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides,
 20 polymorphs, prodrugs, or metabolites wherein Ar, R₁, R₂, W, X, Y, R₃ and R₄ are as defined for Formula I.



Formula II

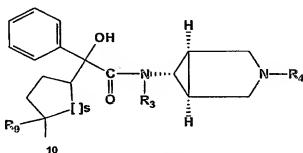
In accordance with a third aspect of the present invention, there are provided compounds having the structure of Formula III and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides,

polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₂, R₃ and R₄ are as defined for Formula I.



Formula III

In accordance with a fourth aspect of the present invention, there are provided compounds having the structure of Formula IV and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, ester, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites wherein R₃ and R₄ are as defined for Formula I, s represents 1 to 2, R₉ is H or F and R₁₀ is F.



Formula IV

In accordance with a fifth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of muscarinic receptor antagonist compounds as described above.

In accordance with a sixth aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of muscarinic receptor antagonist compounds as described above.

In accordance with a seventh aspect of the present invention, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or

disorder of the respiratory system such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, etc.; urinary system which induce such urinary disorders as urinary incontinence, as lower urinary tract symptoms (LUTS), etc.; and gastrointestinal system such as irritable bowel syndrome, obesity, diabetes and
5 gastrointestinal hyperkinesis with compounds as described above, wherein the disease or disorder is associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of compounds as described above.

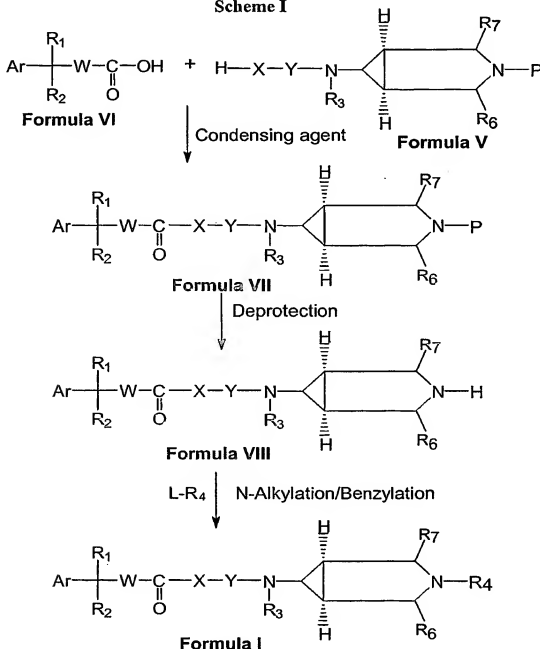
In accordance with an eighth aspect of the present invention, there are provided processes for preparing the compounds as described above.

10 The compounds of the present invention exhibit significant potency in terms of their activity, which was determined by *in vitro* receptor binding and functional assays. Some of the compounds of the present invention were found to be potent muscarinic receptor antagonists with high affinity towards M₃ receptors. Therefore, the present invention provides pharmaceutical compositions for treatment of diseases or disorders
15 associated with muscarinic receptors. Compounds and compositions described herein can be administered orally or parenterally.

DETAILED DESCRIPTION OF THE INVENTION

The compounds described herein may be prepared by techniques well known in the art and familiar to the average synthetic organic chemist. In addition, the compounds described herein may be prepared by the following reaction sequence as shown in Scheme

5 I.

Scheme I

25 The preparation comprises condensing a compound of Formula VI with the compound of Formula V wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), lower perhaloalkyl (C₁-C₄), cyano, hydroxy, nitro, halogen (e.g. F, Cl, Br, I), lower alkoxy (C₁-C₄), lower perhalo- alkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄);

R₁ represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R₂ represents alkyl, C₃-C₇ cycloalkyl ring which any 1-4 hydrogen atoms are substituted with halogen (e.g. F, Cl, Br, I), carbamoyl or lower alkyl;

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR or no atom wherein R represents hydrogen or C₁-C₆ alkyl;

Y represents CHR₅CO wherein R₅ represents hydrogen, methyl or (CH₂)_q wherein q represents 0 to 4;

R₃ represents hydrogen, lower alkyl or CO₂C(CH₃)₃;

R₆ and R₇ are independently selected from H, lower alkyl, COOH, CONH₂, NH₂, or CH₂NH₂; and

P is any group which can be used to protect an amino group, for example, benzyl, t-butyloxy carboxyl, in the presence of a condensing agent to give a protected compound of Formula VII, which on deprotection through reaction with a deprotecting agent in an organic solvent gives an unprotected compound of Formula VIII which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent L-R₄ to give a compound of Formula I wherein L is any leaving group and R₄ represents C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxy, nitro, lower alkoxy carbonyl, halogen, lower alkoxy (C₁-C₄),

lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), or N-lower alkylamino carbonyl (C₁-C₄).

The reaction of the compound of Formula VI with a compound of Formula V to give a compound of formula VII can be carried out in the presence of a condensing agent, for example, 1-(3-dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The reaction of the compound of Formula VI with a compound of Formula V to give a compound of Formula VII can be carried out in a suitable solvent, for example, N,N-dimethylformamide, dimethylsulfoxide, toluene or xylene at a temperature ranging from about 0°C to about 140°C.

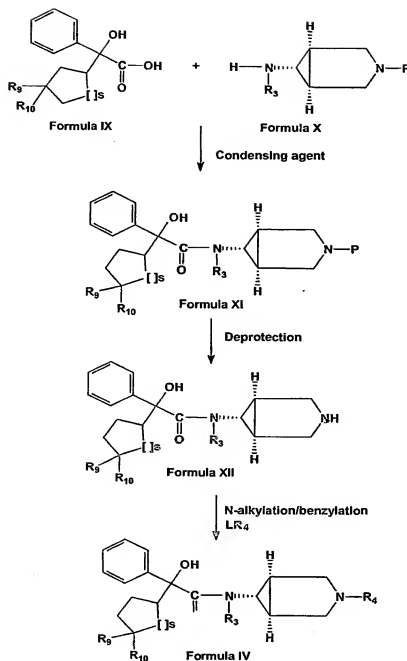
The deprotection of the compound of Formula VII to give a compound of Formula VIII can be carried out with a deprotecting agent, for example, palladium on carbon, trifluoroacetic acid (TFA) or hydrochloric acid.

The deprotection of the compound of Formula VII to give a compound of Formula VIII can be carried out in a suitable organic solvent, for example, methanol, ethanol, tetrahydrofuran or acetonitrile at a suitable temperature ranging from about 10°C to about 50°C.

The N-alkylation or benzylation of the compound of Formula VIII to give a compound of Formula I can be carried out with a suitable alkylating or benzylating agent, L-R₄ wherein L is any leaving group, known in the art, for example, halogen, O-mestyl or O-tosyl group.

The N-alkylation or benzylation of the compound of Formula VIII to give a compound of Formula I can be carried out in a suitable organic solvent such as N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran or acetonitrile, at temperature ranging from about 25°C to about 100°C.

Scheme II



The compound of Formula IV of the present invention may be prepared by the reaction sequence as shown in Scheme II. The preparation comprises condensing a compound of Formula IX (prepared following the procedure described in *J. Med Chem.*, 2000; 43: 5017-5029) wherein R_9 is H or F and R_{10} is F, with the compound of Formula X wherein R_3 represents hydrogen, lower alkyl, or $CO_2C(CH_3)_3$, and P is any group, for example, benzyl, t-butyloxy carbonyl which can be used to protect an amino group, in the presence of a condensing agent to give a protected compound of Formula XI, which on deprotection through reaction with a deprotecting agent in an organic solvent gives an unprotected

compound of Formula XII which is finally N-alkylated or benzylated with a suitable alkylating or benzylating agent, L-R₄ to give a compound of Formula IV wherein L is any leaving group and R₄ represents C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl (C₁-C₄), or lower perhalo alkyl (C₁-C₄), cyano, hydroxy, nitro, lower alkoxycarbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄).

The reaction of the compound of Formula IX with the compound of Formula X to give a compound of Formula XI can be carried out in the presence of a condensing agent, for example, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC) or 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU).

The reaction of the compound of Formula IX with the compound of Formula X to give a compound of Formula XI can be carried out in a suitable solvent, for example, N,N-dimethylformamide, dimethylsulphoxide, toluene or xylene at a temperature ranging from about 0°C to about 25°C.

The deprotection of the compound of Formula XI to give a compound of Formula XII can be carried out in a suitable organic solvent, for example, methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature ranging from about 10°C to about 50°C.

The N-alkylation or benzylation of the compound of Formula XII to give a compound of Formula IV can be carried out with a suitable alkylating or benzylating agent, L-R₄ wherein L is any leaving group, known in the art, for example, halogen, O-mestyl or O-tosyl group.

The N-alkylation or benzylation of the compound of Formula XII to give a compound of Formula IV can be carried out in a suitable organic solvent such as N, N-dimethylformamide, dimethylsulphoxide, tetrahydrofuran or acetonitrile, at temperature ranging from about 0°C to about 100°C.

The conversion of the hydroxyl or oxo group (s) to fluorine atoms(s) normally can be effected by causing the compound to react in an inert solvent which is not detrimental to the reaction, e.g., methylene chloride, chloroform, tetrahydrofuran, acetonitrile, DMSO or in pyridine or in the absence of a solvent, using one equivalent to an excessive amount of fluorinating agent belonging to a class of diethylamino sulphurtrifluoride, at temperatures ranging from about -80°C to about 100°C.

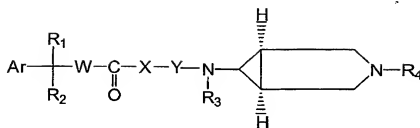
In the above schemes, where specific bases, condensing agents, protecting groups, protecting agents, N-alkylating or benzylating agents, solvents, etc., are mentioned, it is to be understood that other basic condensing agents, protecting group, deprotecting agents, N-alkylating/benzylating agents, solvents, etc., known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

An illustrative list of particular compounds which are capable of being produced by Schemes I & II and shown in Table I include:

- | 15 | COMPOUND NO. | CHEMICAL NAME |
|----|--------------|---|
| | 1. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetamide. |
| | 2. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-(fluorocyclohexyl)-2-hydroxy-2-phenylacetamide. |
| 20 | 3. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide. |
| | 4. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-2[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide. |
| 25 | 5. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide. |
| | 6. | (2R)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide. |
| | 7. | (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide. |

8. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
9. (2R)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
- 5 10. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide.
11. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
12. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or
10 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide.
13. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
14. (2R)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
- 15 15. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide.
16. (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide.

Table-I















5

Formula - III

(wherein W is $(\text{CH}_2)_p$ where $p = 0$, X is no atom and Y is $(\text{CH}_2)_q$ where $q = 0$)

Compound No.	Ar	R ₂	R ₁	R ₃	R ₄
1			OH	H	
2			OH	H	
3			OH	H	
4			OH	H	
5			OH	H	
6			OH	H	
7			OH	H	
8			OH	H	
9			OH	H	
10			OH	H	
11			OH	H	
12			OH	H	

Compound No.	Ar	R ₂	R ₁	R ₃	R ₄
13			OH	H	
14			OH	H	
15			OH	H	
16			OH	H	

Compounds or compositions disclosed may be administered to an animal for treatment orally, or by parenteral route. Pharmaceuticals compositions disclosed herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described herein and/or at least one physiologically acceptable salt addition thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

The present invention also includes within its scope prodrugs of the compounds of Formulae I, II, III, and IV. In general, such prodrugs will be functional derivatives of these compounds, which readily are converted in vivo into the defined compounds. Conventional procedures for the selection and preparation of suitable prodrugs are known.

The present invention also includes the enantiomers, diastereomers, N-oxides, polymorphs, solvates and pharmaceutically acceptable salts of these compounds as well as metabolites having the same type of activity. The present invention further includes pharmaceutical composition comprising the molecules of Formulae I, II, III, and IV or prodrugs, metabolite enantiomers, diastereomers. N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable carrier and optionally included excipients.

The examples mentioned below demonstrate the general synthetic procedure as well as the specific preparation of the particular compound. The examples are provided to

illustrate particular aspects of the disclosure and should not be constrained to limit the scope of the present invention, as defined by the claims.

Experimental Details

- Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane, were dried using various drying reagents according to the procedure described in the literature. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument, Nuclear Magnetic Resonance (NMR) were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

Example 1

- 10 **Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl]-2-[1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No.1).**

Step-a: Synthesis of (2S, 5S)-2-tert-butyl-5-phenyl-1, 3-dioxolan-4-one.

The compound was synthesized following the procedure described in J. Org. Chem., 2000; 65: 6283-6287, using S-(+)-Mandelic acid.

- 15 **Step-b:** Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl-5-phenyl]-1,3-dioxolan-4-one.

- Lithium diisopropylamide (6.9 mmol) was added to a solution of compound of step a (4.6 mmol) in tetrahydrofuran (40 ml) containing 2 ml of hexamethyl phosphoramide and precooled to -78°C under nitrogen atmosphere. The reaction mixture was stirred for 1 hour at the same temperature, and then cyclohexenone (9.2 mmol) diluted with 3 ml of THF was added to the reaction mixture. The mixture was further stirred for 3 hours at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated ammonium chloride and then with water. The organic layer was dried and the residue obtained after removing the solvent was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with 10% ethyl acetate-hexane mixture.

¹HNMR (CDCl₃): 7.67-7.31 (m, 5ArH), 5.42 (d, 1H), 2.48-2.0 (m, 8H), 0.95-0.90 (d, 9H).

IR (DCM): 1714 and 1790 cm⁻¹

Step-c: Synthesis of (2S)-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

- The compound of step b (1 mmol) was dissolved in 5 ml methanol and aqueous sodium hydroxide (3N, 5 ml) was added. The reaction mixture was stirred at room temperature

overnight. The reaction mixture was concentrated under reduced pressure, diluted with water and acidified with concentrated hydrochloric acid. It was extracted with ethyl acetate. The residue obtained after removing the solvents was purified by column chromatography (100-200 mesh, silicagel), eluting the compound with 20% ethyl acetate-hexane mixture.

Step-d: Synthesis of (1 α , 5 α , 6 α)-6-amino-3-benzyl-3-azabicyclo[3.1.0]hexane.

This was synthesized by following the procedure of T.F. Braish, et. al., Synlett. 1100, (1996).

Step-e: Synthesis of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetamide

A solution of compound obtained at step c (1.21 mmol). and (1 α , 5 α , 6 α)-6-amino-3-benzyl-3-azabicyclo[3.1.0]-hexane (1.45 mmol) was dissolved in dimethylformamide (5 ml) and cooled to 0°C. N-methylmorpholine (2.42 mmol) and 1-hydroxybenzotriazole (1.33 mmol) were added to the reaction mixture and stirred for 30 minutes at the same temperature. 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.21 mmol) was added to the reaction mixture and the reaction mixture stirred at 0°C for 1 hour and then at room temperature for 2 days. The reaction mixture was taken in ethyl acetate, washed with water, and dried. The residue obtained after removing the solvent was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with ethyl acetate-hexane mixture.

IR (DCM): 1655 and 1706 cm⁻¹

Example 2

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 2)

Step-a: Synthesis of (2S)-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclohexyl]-5-phenyl-1, 3-dioxalan-4-one.

The compound of Example 1, Step-b (1 mmol) was dissolved in methanol (5 ml) and cooled to 0°C. Sodium borohydride (2 mmol) was added in small lots and the reaction mixture was stirred at 0°C for 1 hour. The solvent was removed under reduced pressure,

the residue taken in ethyl acetate and washed with water. The organic layer was dried and the residue obtained after removal of solvents was used as such.

¹HNMR (CDCl₃): 7.66-7.28 (m, 5ArH), 5.40 (d, 1H), 3.6-3.4 (m, 1H), 2.04 (s, 4H), 1.21 (m, 5H), 0.92 (s, 9H)

5 IR (DCM): 1790 cm⁻¹

Step-b: Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-5-phenyl-1, 3-dioxalan-4-one.

To the compound of step-a (1 mmol) in dichloromethane (10 ml) at 0°C, was added diethylamino sulfur trifluoride (DAST) (1.2 mmol) and the reaction mixture was stirred at
10 room temperature overnight. The reaction mixture was cooled to 0°C and quenched with water. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layer was dried and the residue obtained after removing the solvent was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with ethyl acetate-hexane mixture.

15 m.pt: 136-139°C

¹HNMR (CDCl₃): 7.68-7.26 (m, 5ArH), 5.37 (t, 1H), 4.89 (m, 1H), 2.4 (m, 1H), 2.0-1.24 (m, 6H), 0.89 (d, 9H)

IR (KBr): 1787cm⁻¹

20 **Step-c:** Synthesis of (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenyl acetic acid.

The compound was synthesized following the procedure of Example 1, step-c, using (2S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-5-phenyl-1, 3-dioxalan-4-one instead of (2S)-2-tert-butyl-5-[1R or 1S]-3-oxocyclohexyl]-5-phenyl-1, 3-dioxalan-4-one.

25 **Step-d:** Synthesis of (2S)-(1α, 5α, 6α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide

The title compound was synthesized following the procedure of Example-1, step-e, using (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

30 ¹HNMR (CDCl₃): 7.54-7.19 (m, 10ArH), 4.5 (m, 1H), 3.55 (s, 2H), 3.01 (m, 2H), 2.7 (m, 1H)

IR (KBr): 1656 cm^{-1}

Example 3

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 3)

- 5 **Step-a:** Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1, 3-dioxolan-4-one.

The compound was synthesized following the procedure of Example 1, step-b, using 2-cyclopentenone instead of 2-cyclohexenone.

- ^1H NMR (CDCl_3): 7.70-7.26 (m, 5ArH), 5.40 (d, 1H), 2.88 (m, 1H), 2.37-1.05 (m, 6H),
10 0.90 (s, 9H).

IR (DCM): 1791 and 1746 cm^{-1}

Step-b: Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclopentyl]-5-phenyl-1, 3-dioxolan-4-one.

- The compound was synthesized following the procedure of Example 2, step-a, using (2S,
15 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1, 3-dioxolan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1, 3-dioxolan-4-one.

^1H NMR (CDCl_3): 7.68-7.25 (m, 5ArH), 5.49 (d, 1H), 4.33-4.27 (m, 1H), 2.67-2.62 (m, 1H), 1.97-1.25 (m, 6H), 0.91 (s, 9H).

IR (DCM): 1790 cm^{-1}

- 20 **Step-c:** Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-5-phenyl-1, 3-dioxolan-4-one.

- The compound was synthesized following the procedure of Example 2, step-b, using (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclopentyl]-5-phenyl-1, 3-dioxolan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-hydroxycyclohexyl]-5-phenyl-1, 3-dioxolan-4-one.
25

IR (DCM): 1791 cm^{-1}

Step-d: Synthesis of (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

The compound was synthesized following the procedure of Example 1, step-c, using (2S, 5S)-2-tert-butyl-5-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-5-phenyl-1, 3-dioxolan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1, 3-dioxolan-4-one.

- 5 ¹HNMR (CDCl₃): 7.67-7.25 (m, 5ArH), 5.29-4.99 (m, 1H), 3.29-3.18 (m, 1H), 2.03-1.25 (m, 6H)

IR (DCM): 1726 cm⁻¹

Step-e: Synthesis of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2-(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

- 10 The title compound was synthesized following the procedure of Example 1, step-e, using (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.67-7.19 (m, 10ArH), 5.2 (m, 1H), 3.52 (s, 2H), 3.08-2.97 (m, 6H), 2.33-1.25 (m, 8H).

- 15 IR (DCM): 1653 cm⁻¹

Example 4

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 4A & 4E)

- 20 **Step-a:** Synthesis of (2S, 5S)-2-tert-butyl-5-[1R or 1S)-3,3-difluorocyclohexyl]-5-phenyl-1, 3-dioxolan-4-one.

To a solution of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1,3-dioxolan-4-one (1 mmol) in chloroform cooled to 0°C, was added diethylamino sulfur trifluoride (DAST) (4 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was cooled and quenched with water. The organic layer
25 was separated and the aqueous layer was extracted with dichloromethane. The organic layer was dried and the residue obtained after removal of solvents was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with 5% ethyl acetate-hexane mixture.

- 30 ¹HNMR (CDCl₃): 7.67-6.29 (m, 5ArH), 5.39 (d, 1H), 2.32 (m, 1H), 2.1-1.25 (m, 8H), 0.93 (s, 9H)

IR (DCM): 1792 cm^{-1}

Step-b: Synthesis of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

- 5 The compound was synthesized following the procedure of Example 1, step-c, using (2S)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclohexyl]-5-phenyl-1,3-dioxolan-4-one instead of (2S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1,3-dioxolan-4-one.

m.pt: 144-147°C

IR (KBr): 1694 cm^{-1}

- 10 **Step-c:** Synthesis of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide

The above compound was synthesized following the procedure of Example 1, step-e, using (2S)-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-phenylacetic acid instead of (2S)-2-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

Compound 4A: ^1H NMR (CDCl_3): 7.57-7.13 (m, 10ArH), 3.53 (s, 2H), 2.99 (m, 3H).

- 15 IR (DCM): 1653 cm^{-1}

Compound 4B: ^1H NMR (CDCl_3): 7.59-7.19 (m, 10ArH), 3.53 (s, 2H), 3.06 (m, 3H).

IR (DCM): 1652 cm^{-1}

Compounds 4A & 4B are a pair of diastereomers.

Example 5

- 20 **Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 5A & 5B)**

Step-a: Synthesis of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

- 25 The compound was synthesized following the procedure of Example 4, step-a, using (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1,3-dioxolan-4-one.

^1H NMR (CDCl_3): 7.67-7.25 (m, 5H), 5.42 (s, 1H), 2.80-2.76 (m, 1H), 2.21-1.74 (m, 6H), 0.95 (s, 9H)

IR (DCM): 1793 cm^{-1}

Step-b: Synthesis of (2S)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

- 5 The compound was synthesized following the procedure of Example 1, step-c using (2S)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one instead of (2S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1,3-dioxolan-4-one.

m.pt: 127°C

^1H NMR (CDCl_3): 7.63-7.25 (m, 5H), 3.22-3.10 (m, 1H), 2.26-1.25 (m, 6H).

IR (DCM): 1712 cm^{-1}

- 10 **Step-c:** Synthesis of (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]hexyl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.

The title compound was synthesized following the procedure of Example 1, step-e, using (2S)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

- 15 **Compound 5A**

^1H NMR (CDCl_3): 7.55-7.19 (m, 10ArH), 6.23 (brs, 1H), 3.52 (s, 2H), 3.38 (s, 1H), 3.30-3.22 (m, 1H), 3.06-2.98 (m, 3H), 2.36-2.32 (m, 2H), 2.14-2.04 (m, 4H), 1.56-1.25 (m, 4H)

IR (DCM): 1656 cm^{-1}

Compound 5B

- 20 ^1H NMR (CDCl_3): 7.54-7.19 (m, 10ArH), 6.30 (brs, 1H), 3.52 (s, 2H), 3.37-3.24 (m, 2H), 3.06-2.98 (m, 3H), 2.36-1.25 (m, 10H).

IR (DCM): 1652 cm^{-1}

Compounds 5A and 5B are a pair of diastereomers.

Example 6

Preparation of (2R)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 6)

Step-a: Synthesis of (2R, 5R)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one.

- 5 This compound was synthesized following the procedure described in J. Org. Chem. 2000; 65: 6283-6287.

Step-b: Synthesis of (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

- 10 The compound was synthesized following the procedure of Example 1, step-b, using (2R, 5R)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one instead of (2S, 5S)-2-tert-butyl-5-phenyl-1,3-dioxalan-4-one and 2-cyclopentenone instead of 2-cyclohexenone.

Step-c: Synthesis of (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

- 15 The compound was synthesized following the procedure of Example 4, step-a, using (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxalan-4-one.

¹HNMR (CDCl₃): 7.67-7.25 (m, 5ArH), 5.43 (s, 1H), 2.79-2.76 (m, 1H), 2.23-1.67 (m, 6H), 0.92 (s, 9H)

IR (DCM): 1792 cm⁻¹

- 20 **Step-d:** Synthesis of (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

- 25 The compound was synthesized following the procedure of Example-1, Step-c, using (2R, 5R)-2-tert-butyl-5-[(1R or 1S)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxalan-4-one instead of (2S, 5S)-2-tert-butyl-5-[(1R or 1S)-3-oxocyclohexyl]-5-phenyl-1,3-dioxalan-4-one.

¹HNMR (CDCl₃): 7.64-7.25 (m, 5ArH), 3.22-3.10 (m, 1H), 2.26-1.43 (m, 6H)

IR (KBr): 1724 cm⁻¹

Step-e: Synthesis of (2R)-(1 α , 5 α , 6 α)-6N-[3-benzyl-3-azabicyclo [3.1.0]-hexyl]-2-[1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide.

The title compound was synthesized following the procedure of Example 1, step-e, using (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.54-7.19 (m, 10ArH), 5.77 (brs, 1H), 3.52 (s, 2H), 3.30-2.98 (m, 6H),
2.35-2.31 (m, 2H), 2.13-1.10 (m, 7H).

IR (DCM): 1651cm⁻¹

Example 7

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-2-((3,4-methylenedioxyphenyl)ethyl]-3-azabicyclo[3.1.0]hexyl-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 7)

Step-a: Synthesis of 3,4-methylenedioxyphenethyl bromide.

The compound was synthesized following the procedure described in EP 0388054A1.

Step-b: Synthesis of (1 α ,5 α ,6 α)-6-tert-butoxycarbonylamino-3-azabicyclo[3.1.0]hexane

The compound was synthesized following the procedure described in T.F. Braish et al., Synlett., 1100, (1996).

Step-c: Synthesis of (1 α , 5 α , 6 α)-3N-[2-(3,4-methylenedioxyphenyl)ethyl]-6-[tert-butoxycarbonyl amino]-3-azabicyclo-[3.1.0]hexane

A solution of compound obtained in step b (1.5 mmol) and methylenedioxyphenethyl bromide (1 mmol) in acetonitrile (10 ml) containing potassium carbonate (3 mmol) and potassium iodide (1.5 mmol) was refluxed for 6 hours. The solvent was removed under reduced pressure, the residue was taken in ethyl acetate, and washed with water. The organic layer was then dried and the residue obtained after removal of solvent was purified by column chromatography (100-200 mesh, silica gel), using ethyl acetate-hexane mixture as eluent.

¹HNMR (CDCl₃): 6.72-6.59 (m, 3ArH), 5.9 (s, 2H), 3.12 (d, 2H), 2.75 (s, 1H), 2.54 (m, 4H), 2.36 (d, 2H), 1.43 (d, 1H).

Step-d: Synthesis of (1 α , 5 α , 6 α)-3-N-[2-(3,4-methylenedioxyphenyl)ethyl]-3-azabicyclo[3.1.0]hexane hydrochloride.

The compound of step-c was dissolved in ethyl acetate and ethyl acetate saturated with hydrochloric acid was added to the above reaction mixture and stirred overnight at room

temperature. The solvent was removed under reduced pressure and the residue was washed with hexane and dried.

m. pt: 232 °C

Step-e: Synthesis of (2S)-(1 α ,5 α ,6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)]-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide

A solution of (2S)-[(1R or 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid (1 mmol) and the amine of step-d (1 mmol) in dimethylformamide (5 ml) was cooled to 0°C. Hydroxybenzotriazole (HOBt) (1 mmol) and N-methylmorpholine (4 mmol) were added to the reaction mixture and the reaction mixture was stirred at 0°C for 30 minutes. 1-(3-dimethyl amino propyl)-3-ethyl-carbodiimide hydrochloride was added to the reaction mixture and stirred at 0°C for 1 hour and then at room temperature for 1 day. The reaction mixture was poured into saturated bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, dried and the residue obtained after removal of solvent was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with 50% ethyl acetate-hexane mixture.

¹HNMR (CDCl₃): 7.53-7.3 (m, 5ArH), 6.7-6.58 (m, 3ArH), 5.9 (s, 2H), 3.15 (t, 2H).

IR (KBr): 1662 cm⁻¹

Example 8

20 Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)]-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 8A & 8B)

The title compound was synthesized following the procedure of Example 7, step-e, using (2S)-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid instead of (2S)-[(1R or 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenyl acetic acid.

Compound 8A

¹HNMR (CDCl₃): 7.57-7.26 (m, 5ArH), 6.71-6.58 (m, 3H), 6.30 (brs, 1H), 5.90 (s, 2H), 3.27-2.02 (m, 10H), 1.76-1.23 (m, 8H).

5 Compound 8B

¹HNMR (CDCl₃): 7.54-7.26 (m, 5ArH), 6.70-6.57 (m, 3ArH), 6.32 (brs, 1H), 5.89 (s, 2H), 3.27-2.31 (m, 9H), 1.85-1.25 (m, 10H)

IR (DCM): 1653 cm⁻¹

Compounds 8A and 8B are a pair of diastereomers.

10

Example 9

Preparation of (2R)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 9)

15 The title compound was synthesized following the procedure of Example 7, Step-e, using (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.55-7.26 (m, 5ArH), 6.70-6.57 (m, 3H), 6.30 (brs, 1H), 5.9 (s, 2H), 3.42-2.84 (m, 5H), 2.58-1.39 (m, 13H)

IR (DCM): 1651 cm⁻¹

20

Example 10

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl-2-[1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 10)

25 The title compound was synthesized following the procedure of Example 7, Step-e, using (2S)-(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.54-7.28 (m, 5ArH), 6.7-6.57 (m, 3ArH), 5.89 (s, 2H), 4.5 (m, 1H), 3.13 (t, 2H)

IR (KBr): 1661 cm⁻¹

Example 11

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)]-3-azabicyclo[3.1.0]hexyl-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 11)

- 5 The title compound was synthesized following the procedure of Example 7, Step-e, using (2S)-[1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.54-7.25 (m, 5ArH), 6.70-6.57 (m, 3ArH), 5.92 (s, 2H), 5.29-5.01 (m, 1H), 3.16-2.31 (m, 9H), 2.04-1.25 (m, 10H)

- 10 IR (KBr): 1650 cm⁻¹

Example 12

Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)]-(3-azabicyclo[3.1.0]hexyl-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 12A & 12B)

- 15 **Step-a:** Synthesis of (1 α , 5 α , 6 α)-3-N-(4-methyl-3-pentenyl]-6-t-butoxycarbonyl amino]-3-azabicyclo[3.1.0]hexane.

The compound was synthesized following the procedure of Example 7, Step-c, using 5-bromo-2-methyl pent-3-ene instead of 3,4-dimethylenedioxyphenethyl bromide.

- 20 ¹HNMR (CDCl₃): 5.07 (t, 1H), 4.56 (bs, 1H), 3.10 (d, 1H), 2.76 (s, 1H), 2.36-2.03 (m, 6H), 1.67-1.25 (m, 18H)

IR (KBr): 1706 cm⁻¹

Step-b: Synthesis of (1 α ,5 α ,6 α)-3-N-(4-methyl-3-pentenyl]-3-azabicyclo[3.1.0]hexane hydrochloride

- 25 The compound was synthesized following the procedure of Example 7, step-d, using (1 α , 5 α , 6 α)-3-N-(4-methyl-3-pentenyl]-6-t-butoxycarbonyl amino]-3-azabicyclo[3.1.0]hexane instead of (1 α ,5 α ,6 α)-3-N-[2-(3,4-methylenedioxyphenyl)ethyl]-6-t-butoxycarbonyl amino]-3-azabicyclo[3.1.0] hexane.

m.pt.: 230°C

Step-c: Synthesis of (2S)-(1 α ,5 α ,6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]hexyl-2-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide

A solution of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenyl acetic acid (1 mmol) and compound of step-b, in DMF (5 ml) was cooled to 0 °C. Hydroxy
5 benzotriazole HOBT (1 mmol) and N-methylmorpholine NMM (4 mmol) were added to reaction mixture and stirred for 30 minutes at 0 °C. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC. HCl) was then added to the reaction mixture and stirred for 1 hour at 0 °C followed by stirring at room temperature overnight. The reaction
10 mixture was poured into saturated bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water, dried and the residue obtained after removal of solvents was purified by column chromatography (100-200 mesh, silica gel), eluting the compound with 30% ethyl acetate-hexane mixture.

Compound No. 12A

¹HNMR (CDCl₃): 7.59-7.29 (m, 5ArH), 5.04 (t, 1H), 3.13 (t, 2H)

15 IR (DCM): 1653 cm⁻¹

Compound No. 12E

¹HNMR (CDCl₃): 8.0-7.29 (m, 5ArH), 5.04 (t, 1H), 3.1 (t, 2H)

IR (DCM): 1667 cm⁻¹

Compounds 12A and 12B are a pair of diastereomers.

Example 13

**Preparation of (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]hexyl-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(Compound No. 13A & 13B)**

The compound was synthesized following the procedure of Example 12, step-c, using
25 (2S)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenyl acetic acid instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

Compound 13A

¹HNMR (CDCl₃): 7.60-7.26 (m, 5ArH), 6.30 (brs, 1H), 5.04 (t, 1H), 3.48-2.86 (m, 4H),
2.36-1.40 (m, 21H)

Compound 13B

¹HNMR (CDCl₃): 7.54-7.26 (m, 5ArH), 6.44 (brs, 1H), 5.03 (t, 1H), 3.30-2.85 (m, 4H), 2.41-0.93 (m, 21H)

IR (DCM): 1655 cm⁻¹

- 5 Compounds 13A and 13B are a pair of diastereomers.

Example 14

Preparation of (2S)-(1α, 5α, 6α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 14)

- 10 The compound was synthesized following the procedure of Example 12, step-c, using (2R)-[(1R or 1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenyl acetic acid.

¹HNMR (CDCl₃): 7.58-7.26 (m, 5ArH), 6.30 (brs, 1H), 5.04 (t, 1H), 3.26-2.86 (m, 4H), 2.35-1.25 (m, 20H)

- 15 IR (DCM): 1652 cm⁻¹

Example 15

Preparation of (2S)-(1α, 5α, 6α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide (Compound No. 15)

- 20 The compound was synthesized following the procedure of Example 12, step-c, using (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.6-7.26 (m, 5ArH), 5.01 (m, 2H), 3.11 (s, 2H).

IR (DCM): 1654 cm⁻¹

- 25 **Example 16**

Preparation of (2S)-(1α, 5α, 6α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide (Compound No. 16)

The compound was synthesized following the procedure of Example 12, step-c, using (2S)-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid instead of (2S)-[(1R or 1S)-3,3-difluorocyclohexyl]-2-hydroxy-2-phenylacetic acid.

¹HNMR (CDCl₃): 7.65-7.26 (m, 5ArH), 5.20 (m, 1H), 5.04 (t, 1H), 3.13-2.85 (m, 5H),
2.35-1.25 (m, 19H)

IR (DCM): 1653 cm⁻¹

Biological Activity

Radioligand Binding Assays:

The affinity of test compounds for M₂ and M₃ muscarinic receptor subtypes was determined by [³H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya et al., (Life Sci, 1999,64(25): 2351-2358) with minor modifications.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20 mM, 10 mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500 g for 10 min. The supernatant was subsequently centrifuged at 40,000 g for 20 min. The pellet thus obtained was resuspended in same volume of assay buffer (HEPES 20 mM, EDTA 5 mM, pH 7.4) and were stored at -70°C until the time of assay.

Ligand binding assay: The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein) were incubated in 250 µl of assay buffer (HEPES 20 mM, pH 7.4) at 24-25°C for 3h. Non-specific binding was determined in the presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters (Wallac). The filters were then washed with ice cold 50 mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC₅₀ & K_d were estimated by using the non-linear curve-fitting program using G Pad Prism software. The value of inhibition constant K_i was calculated from competitive binding studies by using Cheng & Prusoff equation (*Biochem Pharmacol*, 1973,22: 3099-3108), K_i = IC₅₀ / (1+L/K_d), where L is the concentration of [³H]NMS used in the particular experiment.

Functional Experiments using isolated rat bladder:**Methodology:**

5 Animals were euthanized by overdose of urethane and whole bladder was isolated and removed rapidly and placed in ice cold Tyrode buffer with the following composition (mMol/L) NaCl 137; KCl 2.7; CaCl₂ 1.8; MgCl₂ 0.1; NaHCO₃ 11.9; NaH₂PO₄ 0.4; Glucose 5.55 and continuously gassed with 95% O₂ and 5 % CO₂.

10 The bladder was cut into longitudinal strips (3 mm wide and 5-6 mm long) and mounted in 10 ml organ baths at 30° C, with one end connected to the base of the tissue holder and the other end connected to a polygraph through a force displacement transducer. Each tissue was maintained at a constant basal tension of 2 g and allowed to equilibrate for 1 hour during which the PSS was changed every 15 min. At the end of equilibration period, the stabilization of the tissue contractile response was assessed with 1μMol/L of Carbachol consecutively for 2-3 times. Subsequently, a cumulative concentration response curve to carbachol (10⁻⁹ mol/L to 3 X 10⁻⁵ mol/L) was obtained. After several washes, once the
15 baseline was achieved, cumulative concentration response curve was obtained in the presence of NCE (NCE added 20 min. prior to the second CRC).

The contractile results were expressed as % of control E max. ED50 values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pKB values were calculated by the formula $pK_B = -\log[(\text{molar concentration of antagonist}/(\text{dose ratio}-1))]$
20 where,

dose ratio = ED50 in presence of antagonist/ED50 in the absence of antagonist.

The results of the in-vitro tests are listed in Table II.

In vitro tests

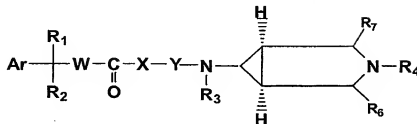
Table-II

Compound No.	Receptor Binding Assay		Functional Assay
	M₂ (pki)	M₃ (pki)	pk_B
6	5.35	6.86	-
9	5.37	7.1	-
11	5.2	7.2	-
12B	4.8	6.2	6.83
13B	<5	5.7	7.17
14	<5	5.8	6.88
16	4.9	6	7.17

5 While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We claim:

1. Compounds having the structure of Formula I:



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1 - C_4), lower perhaloalkyl (C_1 - C_4), cyano, hydroxy, nitro, halogen (e.g. F, Cl, Br, I), lower alkoxy (C_1 - C_4), lower perhalo-alkoxy (C_1 - C_4), unsubstituted amino, N-lower alkylamino (C_1 - C_4) or N-lower alkylamino carbonyl (C_1 - C_4);

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R_2 represents alkyl, C_3 - C_7 cycloalkyl ring in which any 1-4 hydrogen atoms are substituted with halogen (e.g. F, Cl, Br, I), carbamoyl or lower alkyl;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, NR or no atom wherein R represents hydrogen or C_1 - C_6 alkyl;

Y represents CHR_5CO wherein R_5 represents hydrogen, methyl or $(CH_2)_q$ wherein q represents 0 to 4;

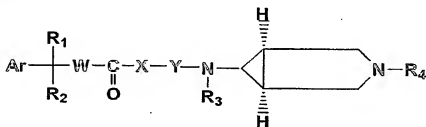
R_3 represents hydrogen, lower alkyl or $CO_2C(CH_3)_3$;

R₆ and R₇ are independently selected from H, lower alkyl, COOH, CONH₂, NH₂, CH₂NH₂; and

R₄ represents C₁-C₁₅ saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxy, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), or N-lower alkylamino carbonyl (C₁-C₄).

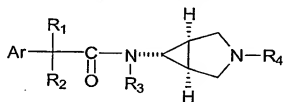
2. A compound according to claim 1 having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar, R₁, R₂, W, X, Y, R₃ and R₄ are as defined for formula I.



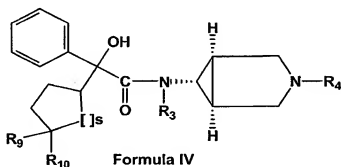
Formula II

3. A compound according to claim 1 having the structure of Formula III and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein Ar, R₁, R₂, R₃ and R₄ are as defined for Formula I.



Formula III

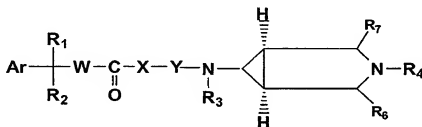
4. A compound according to claim 1 having the structure of Formula IV and its pharmaceutically acceptable salts, esters, enantiomers, diastereomers, N-oxides, prodrugs, or metabolites wherein R_3 and R_4 are as defined for Formula I, and s represents 1 to 2, R_9 is H or F and R_{10} is F.



5. A compound selected from the group consisting of
- (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3-oxocyclohexyl]-2-hydroxy-2-phenylacetamide
 - (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-(fluorocyclohexyl)-2-hydroxy-2-phenylacetamide
 - (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide
 - (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide
 - (2S)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
 - (2R)-(1 α , 5 α , 6 α)-6-N-[3-benzyl-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
 - (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide

- 17 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-
 18 azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-
 19 phenylacetamide
- 20 (2R)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3,4-methylenedioxyphenyl)ethyl)-3-
 21 azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-
 22 phenylacetamide
- 23 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-
 24 azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-
 25 2-phenylacetamide
- 26 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(2-(3, 4-methylenedioxyphenyl)ethyl)-3-
 27 azabicyclo[3.1.0]-hexyl]-2-[(1R or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-
 28 2-phenylacetamide
- 29 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R
 30 or 1S)-3, 3-difluorocyclohexyl]-2-hydroxy-2-phenylacetamide
- 31 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R
 32 or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
- 33 (2R)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-
 34 [(1R or 1S)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
- 35 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R
 36 or 1S, 3R or 3S)-3-fluorocyclohexyl]-2-hydroxy-2-phenylacetamide
- 37 (2S)-(1 α , 5 α , 6 α)-6-N-[3-(4-methyl-3-pentenyl)-3-azabicyclo[3.1.0]-hexyl]-2-[(1R
 38 or 1S, 3R or 3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide.
- 1 6. A pharmaceutical composition comprising a therapeutically effective amount of a
 2 compound as defined in any of claims 1-5 together with pharmaceutically acceptable
 3 carriers, excipients or diluents.

7. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula I,



Formula I

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C₁-C₄), lower perhaloalkyl (C₁-C₄), cyano, hydroxy, nitro, halogen (e.g. F, Cl, Br, I), lower alkoxy (C₁-C₄), lower perhalo-alkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄) or N-lower alkylamino carbonyl (C₁-C₄);

R₁ represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R₂ represents alkyl, C₃-C₇ cycloalkyl ring in which any 1-4 hydrogen atoms are substituted with halogen (e.g. F, Cl, Br, I), carbamoyl or lower alkyl;

W represents (CH₂)_p, where p represents 0 to 1;

X represents an oxygen, sulphur, NR or no atom wherein R represents hydrogen or C₁-C₆ alkyl;

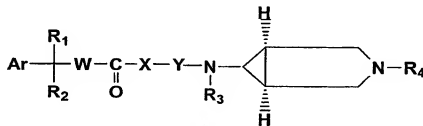
Y represents CHR_5CO wherein R_5 represents hydrogen, methyl or $(\text{CH}_2)_q$ wherein q represents 0 to 4;

R_3 represents hydrogen, lower alkyl or $\text{CO}_2\text{C}(\text{CH}_3)_3$;

R_6 and R_7 are independently selected from H, lower alkyl, COOH , CONH_2 , NH_2 , CH_2NH_2 ; and

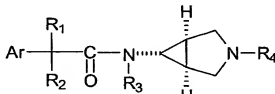
R_4 represents $\text{C}_1\text{-C}_{15}$ saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group may be substituted with lower alkyl ($\text{C}_1\text{-C}_4$), lower perhalo alkyl ($\text{C}_1\text{-C}_4$), cyano, hydroxy, nitro, lower alkoxycarbonyl, halogen, lower alkoxy ($\text{C}_1\text{-C}_4$), lower perhaloalkoxy ($\text{C}_1\text{-C}_4$), unsubstituted amino, N-lower alkylamino ($\text{C}_1\text{-C}_4$), N-lower alkylamino carbonyl ($\text{C}_1\text{-C}_4$).

8. The method according to claim 7 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula II and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein Ar, R_1 , R_2 , W, X, Y, R_3 and R_4 are as defined for Formula I.



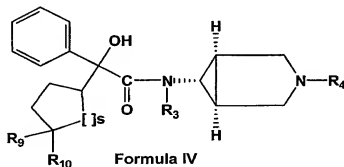
Formula II

9. The method according to claim 7 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula III and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein Ar, R₁, R₂, R₃ and R₄ are as defined for Formula I.



Formula - III

10. The method according to claim 7 for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of a compound having the structure of Formula-IV and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein R₃ and R₄ are as defined for Formula I, s represents 1 to 2, R₉=H or F, and R₁₀=F.



Formula IV

11. The method according to claim 7 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic

obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

12. The method according to claim 8 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

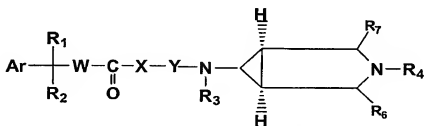
13. The method of claim 9 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

14. The method of claim 10 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

15. The method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, comprising administering to said animal or human, a therapeutically effective amount of the pharmaceutical composition according to claim 6.

16. The method according to claim 15 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis.

17. A process of preparing compounds of Formula I,



Formula I

and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein

Ar represents an aryl or a heteroaryl ring having 1-2 hetero atoms selected from the group consisting of oxygen, sulphur and nitrogen atoms, the aryl or heteroaryl rings may be unsubstituted or substituted by one to three substituents independently selected from lower alkyl (C_1-C_4), lower perhaloalkyl (C_1-C_4), cyano, hydroxy, nitro, halogen (e.g. F, Cl, Br, I), lower alkoxy (C_1-C_4), lower perhalo- alkoxy (C_1-C_4), unsubstituted amino, N-lower alkylamino (C_1-C_4) or N-lower alkylamino carbonyl (C_1-C_4);

R_1 represents a hydrogen, hydroxy, hydroxymethyl, amino, alkoxy, carbamoyl or halogen (e.g. fluorine, chlorine, bromine and iodine);

R_2 represents alkyl, C_3-C_7 cycloalkyl ring in which any 1-4 hydrogen atoms are substituted with halogen (e.g. F, Cl, Br, I), carbamoyl or lower alkyl;

W represents $(CH_2)_p$, where p represents 0 to 1;

X represents an oxygen, sulphur, NR or no atom wherein R represents hydrogen or C_1-C_6 alkyl;

Y represents CHR_5CO wherein R_5 represents hydrogen, methyl or $(CH_2)_q$ wherein q represents 0 to 4;

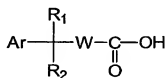
R_3 represents hydrogen, lower alkyl or $CO_2C(CH_3)_3$;

R_6 and R_7 are independently selected from H, lower alkyl, $COOH$, $CONH_2$, NH_2 , CH_2NH_2 ; and

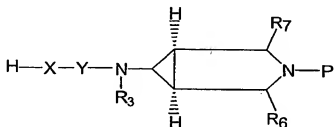
R_4 represents C_1-C_{15} saturated or unsaturated aliphatic hydrocarbon (straight chain or branched) in which any 1 to 6 hydrogen atoms may be substituted with the group independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl

group may be substituted with lower alkyl (C₁-C₄), lower perhalo alkyl (C₁-C₄), cyano, hydroxy, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy (C₁-C₄), lower perhaloalkoxy (C₁-C₄), unsubstituted amino, N-lower alkylamino (C₁-C₄), N-lower alkylamino carbonyl (C₁-C₄), comprising

(a) condensing a compound of Formula VI with a compound of Formula V

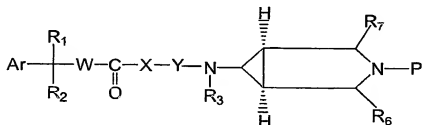


Formula VI



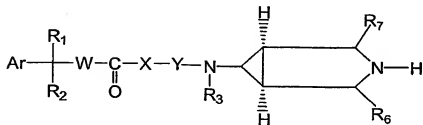
Formula V

wherein Ar, R₁, R₂, W, X, Y, R₃, R₆ and R₇ are as defined earlier for Formula I, to give a protected compound of Formula VII wherein Ar, R₁, R₂, W, X, Y, R₃, R₆ and R₇ are as defined earlier and P is a protecting group for an amino group,



Formula VII

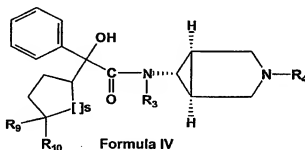
(b) deprotecting the compound of Formula VII in the presence of a deprotecting agent to give an unprotected compound of Formula VIII wherein Ar, R₁, R₂, R₃, W, X, Y, R₃, R₆ and R₇ are as defined earlier, and



Formula VIII

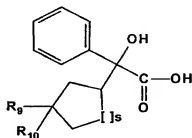
- 58 (c) N-alkylated or benzylated the compound of Formula VIII with a suitable
59 alkylating or benzylating agent to give compounds of Formula I wherein
60 Ar, R₁, R₂, W, X, Y, R₃, R₄, R₆ and R₇ are as defined earlier.
- 1 18. The process according to claim 17 wherein P is selected from the group consisting
2 of benzyl and t-butyloxy carbonyl groups.
- 1 19. The process according to claim 17 wherein the reaction of a compound of formula
2 V with a compound of Formula VI to give compounds of Formula VII is carried
3 out in the presence of a condensing agent selected from the group consisting of 1-
4 (3-dimethyl amino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-
5 diazabicyclo [5.4.0] undec-7-ene 1,8-diazabicyclo [5.4.0] undec-7-ene.
- 1 20. The process according to claim 17 wherein the reaction of a compound of Formula
2 V with a compound of Formula VI to give compounds of Formula VII is carried
3 out in a suitable solvent selected from the group consisting of N,N-
4 dimethylformamide, dimethylsulfoxide, toluene and xylene.
- 1 21. The process according to claim 17 wherein the reaction of a compound of Formula
2 V with a compound of Formula VI is carried out at a temperature ranging from
3 about 0°C to about 140°C.
- 1 22. The process according to claim 17 wherein the deprotection of a compound of
2 Formula VII to give compounds of Formula VIII is carried out with a deprotecting
3 agent selected from the group consisting of palladium on carbon, trifluoroacetic
4 acid (TFA) and hydrochloric acid.
- 1 23. The process according to claim 17 wherein the deprotection of a compound of
2 Formula VII to give compounds of Formula VIII is carried out in a suitable organic
3 solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran
4 and acetonitrile.
- 1 24. The process according to claim 17 wherein the N-alkylation or benzylation of a
2 compound of Formula VIII to give compounds of Formula I is carried out with a
3 suitable alkylating or benzylating agent, L-R₄ wherein L is any leaving group and
4 R₄ is as defined earlier.

- 1 25. The process according to claim 24 wherein the leaving group is selected from the
2 group consisting of halogen, O-mestyl and O-tosyl groups.
- 1 26. The process according to claim 24 wherein the N-alkylation or benzylation of a
2 compound of Formula VIII to give compounds of Formula I is carried out in a
3 suitable organic solvent selected from the group consisting of N,N-
4 dimethylformamide, dimethylsulfoxide, tetrahydrofuran and acetonitrile.
- 1 27. A process of preparing compounds of Formula IV,

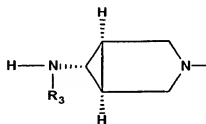


3 and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates,
4 esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs, or
5 metabolites, wherein R_3 represents hydrogen, lower alkyl or $\text{CO}_2\text{C}(\text{CH}_3)_3$; R_4
6 represents $\text{C}_1\text{-C}_{15}$ saturated or unsaturated aliphatic hydrocarbon (straight chain or
7 branched) in which any 1 to 6 hydrogen atoms may be substituted with the group
8 independently selected from halogen, arylalkyl, arylalkenyl, heteroarylalkyl or
9 heteroarylalkenyl having 1 to 2 hetero atoms selected from the group consisting of
10 nitrogen, oxygen and sulphur atoms with an option that any 1 to 3 hydrogen atoms
11 on an aryl or heteroaryl ring in said arylalkyl, arylalkenyl, heteroarylalkenyl group
12 may be substituted with lower alkyl ($\text{C}_1\text{-C}_4$), lower perhalo alkyl ($\text{C}_1\text{-C}_4$), cyano,
13 hydroxy, nitro, lower alkoxy, carbonyl, halogen, lower alkoxy ($\text{C}_1\text{-C}_4$), lower
14 perhaloalkoxy ($\text{C}_1\text{-C}_4$), unsubstituted amino, N-lower alkylamino ($\text{C}_1\text{-C}_4$), N-lower
15 alkylamino carbonyl ($\text{C}_1\text{-C}_4$); s represents 1 to 2, R_9 is H or F and R_{10} is F,
16 comprising

- (a) condensing a compound of Formula IX with a compound of Formula X

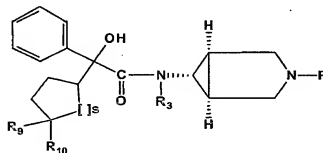


Formula IX



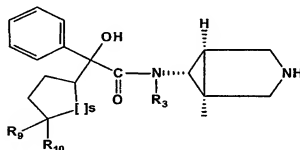
Formula X

wherein R_3 and R_4 are as defined earlier for Formula I, s represents 1 to 2, R_9 is H or F and R_{10} is F, to give a protected compound of Formula XI wherein R_3 , R_4 , s , R_9 and R_{10} are as defined earlier and P is a protecting group for an amino group,



Formula XI

- (b) deprotecting the compound of Formula XI in the presence of a deprotecting agent to give an unprotected compound of Formula XII wherein R_3 , R_4 , s , R_9 and R_{10} are as defined earlier, and



Formula XII

- (c) N-alkylated or benzylated the compound of Formula XII with a suitable alkylating or benzylating agent to give compounds of Formula IV wherein R_3 , R_4 , s , R_9 and R_{10} are as defined earlier.

- 1 28. The process according to claim 27 wherein P is selected from the group consisting
2 of benzyl and t-butyloxy carbonyl groups.
- 1 29. The process according to claim 27 wherein the reaction of a compound of Formula
2 IX with a compound of Formula X to give compounds of Formula XI is carried out
3 in the presence of a condensing agent selected from the group consisting of 1-(3-
4 dimethylamino propyl)-3-ethyl carbodiimide hydrochloride (EDC) and 1,8-
5 diazabicyclo [5.4.0] undec-7-ene (DBU).
- 1 30. The process according to claim 27 wherein the reaction of a compound of Formula
2 IX with a compound of Formula X to give compounds of Formula XI is carried out
3 in a suitable solvent selected from the group consisting of N,N-
4 dimethylformamide, dimethylsulfoxide, toluene and xylene.
- 1 31. The process according to claim 27 wherein the reaction of a compound of Formula
2 IX with a compound of Formula X is carried out at a temperature ranging from
3 about 0°C to about 140°C.
- 1 32. The process according to claim 27 wherein the deprotection of compound of
2 Formula XI to give compounds of Formula XII is carried out with a deprotecting
3 agent selected from the group consisting of palladium on carbon, trifluoroacetic
4 acid (TFA) and hydrochloric acid.
- 1 33. The process according to claim 27 wherein the deprotection of a compound of
2 Formula XI to give compounds of Formula XII is carried out in a suitable organic
3 solvent selected from the group consisting of methanol, ethanol, tetrahydrofuran
4 and acetonitrile.
- 1 34. The process according to claim 27 wherein the N-alkylation or benzylation of a
2 compound of Formula XII to give compounds of Formula IV is carried out with a
3 suitable alkylating or benzylating agent, L-R₄ wherein L is any leaving group and
4 R₄ is as defined earlier.
- 1 35. The process according to claim 34 wherein the leaving group is selected from the
2 group consisting of halogen, O-mestyl and O-tosyl groups.

- 1 36. The process according to claim 34 wherein the N-alkylation or benzylation of a
2 compound of Formula XII to give compounds of Formula IV is carried out in a
3 suitable organic solvent selected from the group consisting of N,N-
4 dimethylformamide, dimethylsulfoxide, tetrahydrofuran and acetonitrile.

INTERNATIONAL SEARCH REPORT

International Search No
PCT/IB 03/01327

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/52 A61K31/403 A61P1/12 A61P3/10 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 034 082 A (MARCHINGTON ALLAN PATRICK ET AL) 7 March 2000 (2000-03-07) column 2, formula (I) column 9, line 17 - line 31	1-36
Y	US 5 948 792 A (KAWAKAMI KUMIKO ET AL) 7 September 1999 (1999-09-07) cited in the application column 2, formula (I) column 9, line 17 - line 31	1-36

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

Date of the actual completion of the international search

13 November 2003

Date of mailing of the international search report

26/11/2003

Name and mailing address of the ISA

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Fax (+31-70) 340-3016

Authorized officer

Hoepfner, W

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/IB 03/01327**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 7-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/IB 03/01327

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